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Ethanol-induced Back-Diffusion of H^+ in Rat Stomach

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Ethanol causes mucosal injury to the stomach and which accompanied by back-diffusion of H^+. Using several drugs known to modify the gastric acid secretion and to provide cytoprotection, the effect of back-diffusion of H^+ by ethanol was examined. Following 48 hours of starvation rats were anesthetized with urethane, and their stomachs were filled with 4 ml of 20% ethanol solution containing 1.8 mM HCl (7.2 μEq/4 ml) every 15 min. H^+ content of the collected perfusates was determined by back-titration to pH 6.0. The presence of ethanol in the stomach for 1 hour caused a loss of luminal H^+ at a rate of 4.8±0.4 μEq/15 min. Pretreatment of rats with atropine (2 mg/Kg, i.v.), pirenzepine (2 mg/Kg, i.v.), cimetidine (10 mg/Kg, i.v.), cromolyn sodium (20 mg/Kg/hr, i.v.) or domperidone (1 mg/Kg, i.v.) did not affect the ethanol-induced H^+ back-diffusion. Similarly, no effect was seen in rats treated with prostaglandin E_2 (100μg/Kg, i.v.) or indomethacin (5 mg/Kg, s.c.). The addition of procaine (10^{-5}∼10^{-3} M) or propranolol (10^{-9}∼10^{-5} M) to the perfusate did not cause any changes in the ethanol-induced H^+ back-diffusion. However, pretreatment of rats with acetazolamide (100 mg/Kg, i.v.) or ethoxzolamide (50 mg/Kg/day, p.o. for 6 days), carbonic anhydrase inhibitors, markedly suppressed the ethanol-induced loss of luminal H^+. Based on these results, it is suggested that ethanol-induced back-diffusion of H^+ is mediated, at least in part, by the activity of carbonic anhydrase, and that cholinergic, histaminergic and dopaminergic mechanisms are not involved. Moreover, the implications of prostaglandins and membrane stability are not suggested.

Key Words: Ethanol, H^+ back-diffusion, gastric acid secretion, cytoprotection, carbonic anhydrase inhibitor

In 1833, when William Beaumont first observed the classical signs of inflammatory changes in the gastric mucosa of his gastrostomized patient, he called attention to the development of acute gastritis following the oral ingestion of ethanol. Similar results were observed in some animals as well as in humans (Chey 1972). The mechanism of gastric mucosal injury caused by the presence of an ethanol solution, however, has not been adequately investigated until recently. Davenport (1967), using Heidenhain pouches in dogs, found that ethanol solutions diluted to 8% or less did not damage the mucosal barrier of the stomach. However, ethanol solutions diluted to 14 and 27% broke the barrier. Along with this change, there was an increased insorption of H^+ and an increased exsorption of Na^+ and K^+. This observation suggested that ethanol could alter the physiological functions of the mucosal barrier, resulting in an increased back-diffusion of H^+ through the damaged mucosa. In rats, gastric acid secretion was inhibited by increasing the concentration of ethanol solution up to 10% and ethanol concentrations greater than above 20% induced the loss of acid from the stomach by the back-diffusion of H^+ through the gastric muscosa (Puurunen 1978). Kim *et al.* (1981) confirmed this and proved that this inhibitory effect of ethanol on gastric acid secretion is due to the back-diffusion of H^+ induced by ethanol.

Robert *et al.* (1979) observed that prostaglandins prevent the formation of gastric mucosal lesions inducible in rats by a variety of necrotizing agents including absolute ethanol. This property of prostaglandins is called cytoprotection. Such a protective effect was observed without reducing the gastric acid secretion. In addition there were observations that the presence of irritative concentrations

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of ethanol within the stomach lumen provided an adaptive cytoprotection of gastric mucosa from the damage followed by the administration of absolute ethanol (Robert *et al.* 1983).

There have been numerous studies concerning the effect of ethanol on the gastric mucosa. However, little is known about the underlying mechanism of back-diffusion of H^+ from the lumen by ethanol. We have examined the effects of several drugs known to modify gastric acid secretion and to provide cytoprotection on the back-diffusion of H^+ induced by ethanol.

MATERIALS AND METHODS

Animals

Albino rats of either sex weighing about 200g were used. After 1 week adaptation period, experiments were performed on rats which have been fasted for 48 hours but were allowed the water *ad libitum*.

Surgical procedure

Rats were anesthetized by a subcutaneous administration of urethane (1.5 g/Kg). The trachea was cannulated, and two polyethylene cannulas were introduced into the stomach for the gastric perfusion system; the esophageal cannula was placed in the cardiac region through an esophageal incision and the duodenal cannula was placed in the pyloric region through an incision in the duodenum. Another polyethylene cannula was inserted into the jugular vein for the administration of drugs. Rats were then allowed to stabilize for one hour after surgery, during which time the stomach was perfused with 4 ml of saline (pH 6.0) every 15 min.

Measurement of gastric acid secretion

The secretion of gastric acid was determined by using the gastric perfusion system. Briefly, 4 ml portions of the perfusion solution were introduced into the stomach as a bolus via the esophageal cannula every 15 min. Samples were collected every 15 minutes from a duodenal cannula and titrated to pH 6.0 with an automatic potentiometric titrator (TTT_2b, Radiometer, Copenhagen). Gastric acid output was expressed in μEq/15 min.

Perfusion solutions

Physiological saline adjusted to pH 6.0 was used as the standard perfusion solution, and the basal level of gastric acid secretion was determined from the effluent of this standard perfusion solution. Subsequently, saline containing 1.8 mM HCl was introduced into the stomach. The effluent of this perfusion solution was titrated back to pH 6.0 (original saline pH) to determine the amount of additional gastric acid secretion. To determine the ethanol dependent back-diffusion of H^+, 20% (V/V) ethanol solution (in saline) containing 1.8 mM HCl was introduced into the stomach and the effluent obtained from this perfusion was tested for the remaining amount of H^+.

Drugs

Ethanol absolut (Merck, Germany); prostaglandin E_2 (Upjohn, USA); indomethacin (Sigma, USA); atropine sulfate (Merck, Germany); pirenzepine (Boehringer Ingelheim, Germany); acetazolamide (Lederle Laboratory, USA); ethoxzolamide (Upjohn, USA); cromolyn sodium (Sigma, USA); cimetidine (Il Yang, Korea); procaine hydrochloride (Kook Jei, Korea); propranolol (Sigma, USA); domperidone (Yuhan, Korea)

RESULTS

1. Effect of ethanol on the loss of acid from the gastric lumen

When the stomach was perfused with a standard perfusion solution (saline, pH 6.0), the secretion of gastric acid stabilized within 60 min. Thereafter, saline containing 1.8 mM HCl was perfused for 90 min and then 20% ethanol solution (in saline) containing the same concentration of hydrogen ions was perfused for 60 min. Just prior to perfusion of the ethanol solution, the acid output was 8.97±0.35 μEq/15 min, and during the 60 min ethanol perfusion a loss of up to 5.31±0.41 μEq/15 min of acid from the gastric lumen occured. At this time acid output was 3.65±0.48 μEq/15 min which was lower than the amount of acid added to the perfusion solution (7.2 μEq/15 min). After cessation of the ethanol perfusion, acid output recovered within 60 min by perfusing with 1.8 mM HCl in saline. Following such recovery, the standard perfusion solution was perfused again for 60 min to determine whether the ability of the mucosa to secrete acid was still intact (Fig. 1).

2. Effect of anticholinergics on the ethanol-induced loss of acid

Atropine (2 mg/Kg) or pirenzepine (2 mg/Kg) were injected intravenously through the jugular vein 30 min

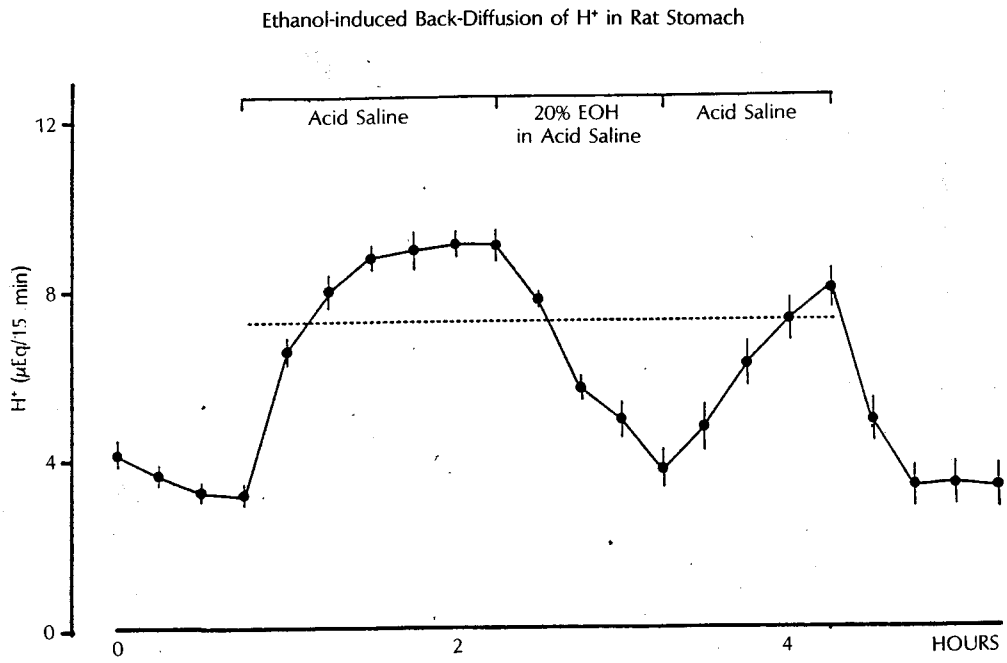

Fig. 1. Effect of ethanol (20%) on the loss of H+ from perfused rat stomach. Saline or acid saline (1.8 mM HCl in saline) was perfused into the stomach at 15 min intervals. The level of the dotted line is the acidity of the acid saline (7.2 μEq/4ml).

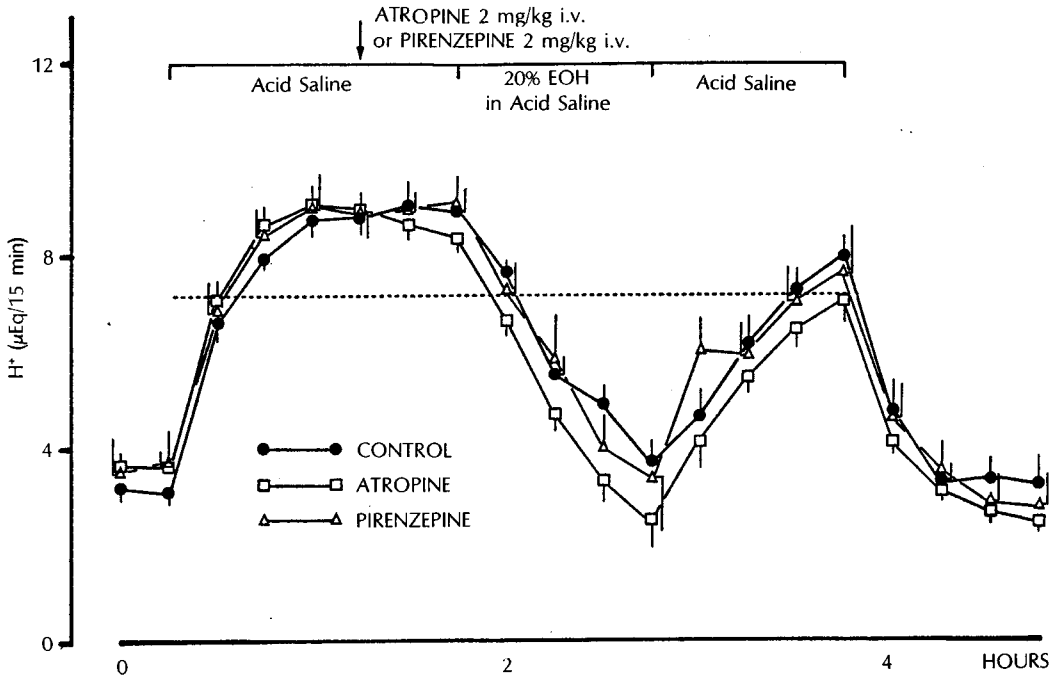

Fig. 2. Effect of atropine or pirenzepine on the ethanol-induced loss of H+ from perfused rat stomach. Saline or acid saline (1.8 mM HCl in saline) was perfused into the stomach at 15 min intervals. The level of the dotted line is the acidity of the acid saline (7.2 μEq/4 ml).

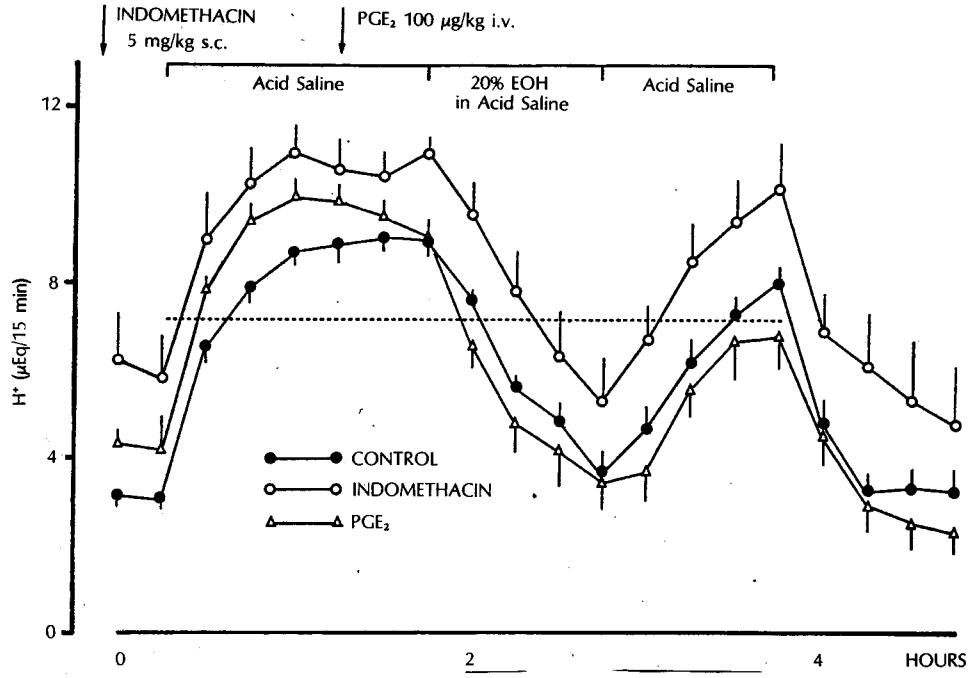

Fig. 3. *Effect of prostaglandin E_2 or indomethacin on the ethanol-induced loss of H^+ from perfused rat stomach. Saline or acid saline (1.8 mM HCl in saline) was perfused into the stomach at 15 min intervals. The level of the dotted line is the acidity of the acid saline (7.2 μEq/4 ml).*

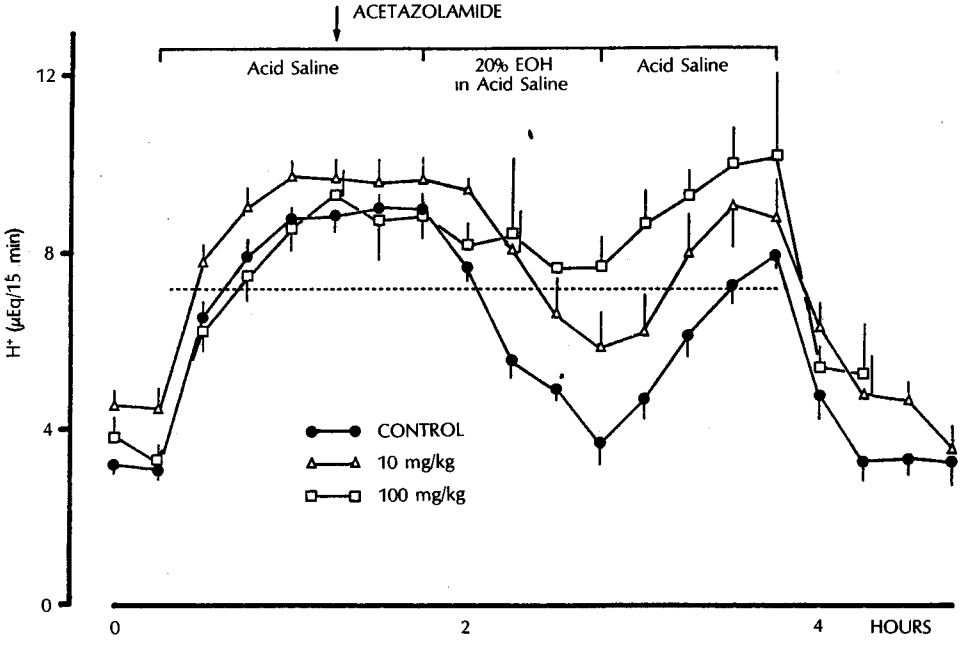

Fig. 4. *Effect of acetazolamide on the ethanol-induced loss of H^+ from perfused rat stomach. Saline or acid saline (1.8 mM HCl in saline) was perfused into the stomach at 15 min intervals. The level of the dotted line is the acidity of the acid saline (7.2 μEq/4 ml).*

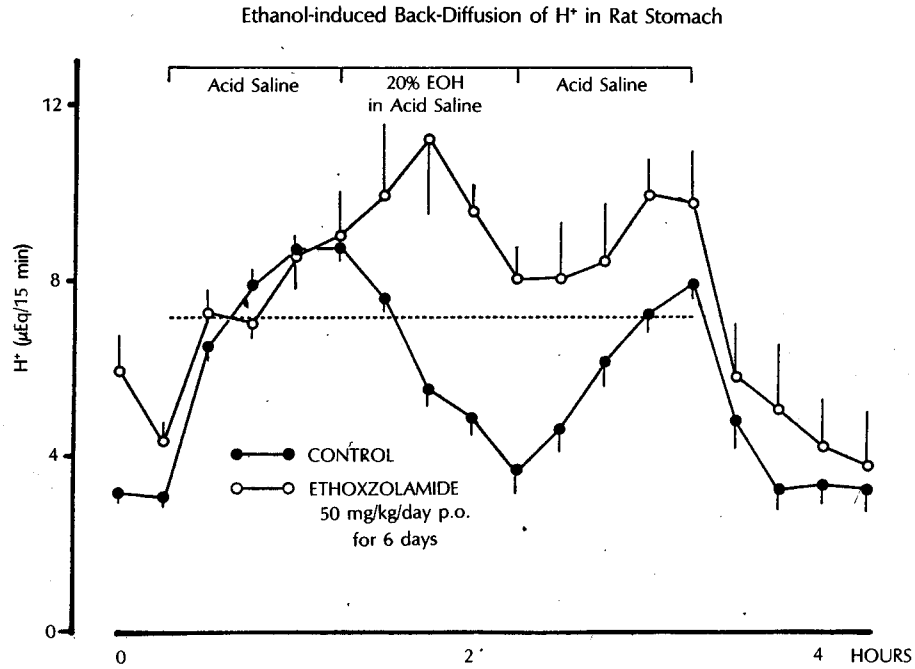

Fig. 5. *Effect of ethoxzolamide on the ethanol-induced loss of H+ from perfused rat stomach. Saline or acid saline (1.8 mM HCl in saline) was perfused into the stomach at 15 min intervals. The level of the dotted line is the acidity of the acid saline (7.2 μEq/4 ml).*

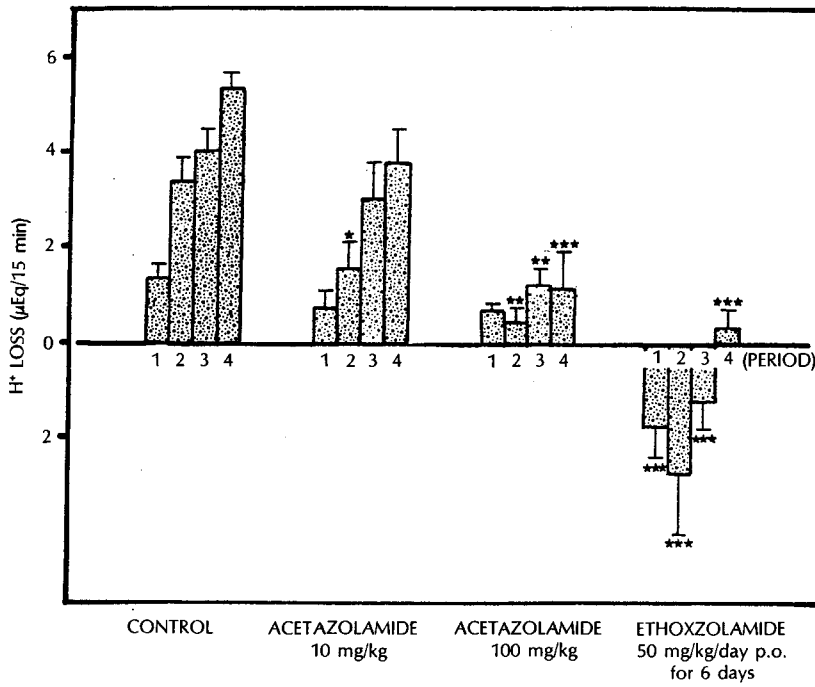

Fig. 6. *Effect of acetazolamide or ethoxzolamide on the ethanol-induced loss of H+ from perfused rat stomach. Ethanol was administered for 60 min (sum of four 15 min periods). *p<0.05, ** p<0.01, *** p<0.001 (difference from corresponding period of the control group)*

prior to ethanol perfusion. Pretreatment with atropine or pirenzepine did not affect the ethanol-induced loss of acid from the stomach (Fig. 2.).

3. Effects of histamine inhibitors, dopamine antagonists or membrane stabilizers on the ethanol-induced loss of acid

Thirty minutes prior to ethanol perfusion, cimetidine (10 mg/Kg) was injected intravenously or cromolyn sodium was administered by intravenous infusion (20 mg/Kg/hr) for 2.5 hr. Administrations of cimetidine or cromolyn sodium did not affect the ethanol-induced loss of acid from the stomach.

Domperidone (1 mg/Kg) was injected intravenously 30 min prior to ethanol perfusion. Pretreatment with domperidone did not affect the ethanol-induced loss of acid.

Procaine (10^{-5}~10^{-3} M) or propranolol (10^{-9}~10^{-5} M) were administrered locally to the gastric mucosa for 1.5 hr by adding them directly to the perfusion solution. Perfusion with these perfusion solutions was started 30 min prior to ethanol perfusion. Local administration of procaine or propranolol did not affect the ethanol-induced loss of acid.

4. Effect of prostaglandins on the ethanol-induced loss of acid

Prostaglandin E_2 (100 μg/Kg) was injected intravenously 30 min prior to ethanol perfusion and in another experiment indomethacin (5 mg/Kg) was injected subcutaneously 2.5 hr before ethanol perfusion. Indomethacin pretreatment caused an increase in acid output throughout the perfusion experiment. However the ethanol-induced loss of acid was not affected by pretreatment with indomethacin or prostaglandin E_2 (Fig. 3).

5. Effect of carbonic anhydrase inhibitors on the ethanol-induced loss of acid

Acetazolamide, a known inhibitor of carbonic anhydrase, was injected intravenously 30 min prior to ethanol perfusion in 2 doses, 10 mg/Kg and 100 mg/Kg. Pretreatment with acetazolamide at a dose of 10 mg/Kg slightly decreased the ethanol-induced loss of acid. With a large dose of 100 mg/Kg, however, the ethanol-induced loss of acid was markedly inhibited from the 2nd period of ethanol perfusion (ethanol was perfused for 60 min in four 15 min periods) (Fig. 4, Fig. 6, Table 1). Pretreatment with ethoxzolamide (50 mg/Kg/day, P.O., for 6 days), another carbonic anhydrase inhibitor, produced a complete blockade of the ethanol-induced loss of acid (Fig. 5, 6, Table 1).

Table 1. Effects of several drugs on the ethanol (20%)-induced loss of H^+ from the perfused effluent of rat stomachs

Treatment	Dose	No.of Exp.	H^+ loss (μEq/15 min)
Control		11	5.31±0.46
Atropine	2 mg/kg, i.v.	12	5.72±0.66
Pirenzepine	2 mg/kg, i.v.	7	5.93±0.99
Cimetidine	10 mg/kg, i.v.	5	6.26±0.57
Cromolyn sodium	20 mg/kg/hr, i.v.	4	6.56±0.60
Domperidone	1 mg/kg, i.v.	4	5.42±0.86
Prostaglandin E_2	100 μg/kg, i.v.	8	6.05±0.48
Indomethacin	5 mg/kg, s.c.	8	5.73±1.41
Procaine	10^{-5} M,perfusion	4	6.77±0.98
	10^{-4} M,perfusion	5	5.47±0.71
	10^{-3} M,perfusion	5	5.54±0.87
Propranolol	10^{-9} M,perfusion	5	4.38±0.96
	10^{-7} M,perfusion	5	6.86±1.14
	10^{-5} M,perfusion	4	6.46±1.59
Acetazolamide	10 mg/kg, i.v.	7	3.78±0.77
	100 mg/kg, i.v.	4	1.32±0.79***
Ethoxzolamide	50 mg/kg/day p.o. for 6 days	5	0.31±0.49***

Values are means ± S.E. of 4th period of ethanol perfusion. Ethanol was perfused for 60 min (sum of four 15 min periods).
*** $p<0.001$ (difference from the control group).

DISCUSSION

Hydrogen ion absorption occurs rapidly in various parts of the gastrointestinal tract, but the stomach has the unique ability to retain the acid solution. This remarkable ability of the stomach to maintain H^+ gradient is achieved by a barrier against the absorption of hydrogen ions (Ivey 1971). Although the existence of a gastric mucosal barrier was first postulated by Teorell in 1933, the concept aroused little attention. In 1964, Davenport suggested that the application of various damaging agents including ethanol caused a loss of H^+ from the lumen by an increased H^+ back-diffusion out of the lumen and an increased net flux of Na^+ into the lumen. So this damage was portrayed as an increased mucosal permeability to ions (Davenport 1966).

Increased mucosal permeability could also account for the rapid decline in the potential difference following damage induced by ethanol (Rehm and Hokin 1947; Bigerstaff and Leitch 1977), as ions moved passively down the electrochemical gradient. In addition to this important property, ethanol has many other complex actions related to gastric functions.

These include inhibition of active H^+ secretion (Sernka *et al.* 1974; Puurunen 1978; Kim *et al.* 1981) and mucus synthesis (Garner *et al.* 1983), increased histamine secretion (Soper and Tepperman 1979; Tepperman and Soper 1979), increased bicarbonate secretion (Swierczek and Konturek 1981; Dayton *et al.* 1983), increased prostaglandins secretion (Collier 1975; Konturek *et al.* 1982; Robert *et al.* 1983), decreased carbonic anhydrase activity (Newsome and Leitch 1978) and decreased ethanol absorption upon repeated treatments with ethanol (Deregnaucourt and Code 1979). Based on these actions, ethanol may exhibit both gastric mucosal damage and protection. In preliminary experiments, although we attempted to perfuse with 20% ethanol in a standard perfusion solution (saline, pH 6.0), we could not titrate the acid in the collected perfusate because the pH of the effluent was above 6.0. It is then suggested that an increased H^+ loss accompanied by bicarbonate secretion contributed to this effect. When 20% ethanol solution containing 1.8 mM HCl was perfused, the acid content in the effluent was lower than the added acid to the perfusion solution. This suggests that H^+ back-diffusion has occurred by topical application of 20% ethanol solution to the gastric mucosa. We have therefore studied the mode of this ethanol-induced H^+ back-diffusion in the gastric mucosa of rats by using several drugs known to modify H^+ transport or cytoprotection.

Prostaglandins are known to inhibit gastric acid secretion (Robert *et al.* 1967) and to prevent of ulcer formation (Robert *et al.* 1968; Robert *et al.* 1976; Gibinski *et al.* 1977). It was thus assumed that this antiulcer effect was due to an inhibition of gastric acid secretion. In further studies, Robert *et al.* (1979) demonstrated that administration of the prostaglandin E and F series provided protection in a dose-dependent manner against the gastric necrosis produced by absolute ethanol and other necrotizing agents without inhibiting acid secretion. Thus they concluded that prostaglandins might have a specific ability to protect the gastric mucosa which is unrelated to a reduction of acid secretion, and this phenomenon was then called cytoprotection. The cytoprotective effect of prostaglandins has been suggested to be mediated by stimulations of bicarbonate secretion (Garner *et al.* 1979; Kauffman *et al.* 1980; Garner *et al.* 1983), stimulation of mucus glycoprotein transport (Parke *et al.* 1975), better maintenance of mucosal blood flow (Kauffman *et al.* 1980; Cheung 1980; Leung *et al.* 1985), stimulation of mucosal growth (Schmidt *et al.* 1985) and reduction in gastric mucosal histamine (Soper and Tepperman 1979). However little is known about the underlying mechanisms involved in the cytoprotective effect of prostaglandins on gastric mucosal integrity. In this context, Puurunen (1980) demonstrated that prostaglandin E_2 effectively protected the gastric mucosa against ethanol-induced ulceration without any significant decline in the back-diffusion of H^+ ions from the gastric lumen. Swierczek and Konturek (1981) have also shown that 16, 16-dimethyl prostaglandin E_2 did not prevent the fall of the transmucosal potential difference normally inducible by mucosal barrier breakers. In the present study neither prostaglandin E_2 nor indomethacin affected the ethanol-induced H^+ back-diffusion. This finding is compatible with the results of Puurunen (1980) or Swierczek and Konturek (1981). Pirenzepine, a newly developed cholinergic M_1 receptor antagonist (Hammer *et al.* 1980), is also known to have a weak cytoprotective property (Konturek *et al.* 1982). However pirenzepine also had no influence on the ethanol-induced loss of H^+ in the present study. It is therefore suggested that the cytoprotective effect produced by prostaglandins or pirenzepine is not mediated by reductions of H^+ back-diffusion.

We have also examined whether the ethanol-induced loss of H^+ from the gastric lumen is influenced by other pathways (cholinergic, histaminergic, dopaminergic) which also control gastric secretory function (Caldara *et al.* 1978; Baron 1983). However, the agents affecting the cholinergic, histaminergic or dopaminergic systems had no infuence on the ethanol-induced loss of H^+. Furthermore, even with the agents known to affect membrane stability, such as procaine (Skou 1961) or propranolol (Tarr *et al.* 1973) the ethanol induced loss of H^+ from the gastric lumen was not influenced.

In the oxyntic cells of the stomach, as a result of the separation of H_2O into H^+ and OH^- and secretion of HCl through the apical membrane, OH^- accumulates. This accumulated OH^- is combined with CO_2 to form HCO_3^- in the presence of carbonic anhydrase. This HCO_3^- can, in turn, be exchanged with Cl^- at the basolateral membrane. In this manner, carbonic anhydrase plays a vital role in oxyntic cells, so that they can secrete H^+ and can maintain a neutral pH as well as other metabolic functions (Forte *et al.* 1980; Dayton *et al.* 1983). Vinik and Heldsinger (1984) reported that gastric secretagogues such as gastrin, histamine or carbamylcholine caused a dose-dependent increase in carbonic anhydrase activity in oxyntic cells. The ability of these secretagogues to stimulate carbonic anhydrase was inhibited by the carbonic anhydrase inhibitor, acetazolamide. This finding suggests that carbonic anhydrase is necessary for the production of H^+ and HCO_3^-. Bicarbonate, formed by carbonic anhydrase, contributes to the protection of the gastric mucosa against luminal acid by forming

an unstirred alkaline layer within the mucus gel and also acts as an intracellular buffer within epithelial cells (Kivilaakso 1985). Inhibition of carbonic anhydrase activity by acetazolamide was reported to inhibit the secretion of gastric HCO_3^- and to enhance the susceptibility to ulceration in rats (Kollberg *et al.* 1981; Cho *et al.* 1984), dogs (Werther *et al.* 1965), rabbits and isolated frog gastric sacs (Kivilaakso and Silen 1981). However, Robert *et al.* (1982) observed that acetazolamide may prevent gastric lesions induced by necrotizing agents such as absolute ethanol. Konturek *et al.* (1983) extended this finding and reported that acetazolamide prevented the ethanol-induced gastric lesions in a dose-dependent manner, and that this effect was accompanied by an increased biosynthesis of mucosal prostaglandins. In patients with gastric and duodenal ulcers, acetazolamide induced a strong and constant decrease of both basal and histamine stimulated gastric acid secretion and enhanced healing rates (Puşcaş 1984; Valean *et al.* 1984).

In the present study acetazolamide, but not prostaglandin E_2, prevented the ethanol-induced loss of H^+ from the gastric lumen. This effect of the carbonic anhydrase inhibitor was confirmed by using another carbonic anhydrase inhibitor, ethoxzolamide. Thus it is suggested that the ethanol- induced back-diffusion of H^+ is mediated, at least in part, by the activity of carbonic anhydrase, and also suggested that the protective effect of a carbonic anhydrase inhibitor may be mediated by the prevention of H^+ back-diffusion. However, the precise mechanism remains to be elucidated.

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